REMARKS

A. Status of the Claims

Prior to the submission of this paper, claims 1-55 were pending, with claims 1-11, 42-46, and 52 under examination and claims 12-41, 47-51, and 53-55 withdrawn. In this paper, Applicants have requested the cancellation of claim 52 without prejudice or disclaimer. When this claim cancellation has been entered, the claims under examination will be claims 1-11 and 42-46.

Claim 1-11, 42-46, and 52 are rejected under 35 U.S.C. § 112, ¶ 1 for allegedly containing new matter.

Claim 1-11, 42-46, and 52 are rejected under 35 U.S.C. § 112, ¶ 2, for allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1, 2, 5, 6, 10, 11, 42, and 44 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Pre-Grant Publication No. 2001/0048929 to Chong et al. ("Chong") in view of an article by Paoletti et al. in *Infect. Immun.* 62:3236-3243, 1994 ("Paoletti (1994)").

Claims 9 and 52 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong, in view of Paoletti (1994), and in further view of an article by Wang et al. published in *PNAS* 95:6584-6589, 1998) ("Wang").

Claims 3 and 4 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong, in view of Paoletti (1994), and in further view of an article by Paoletti et al. published in *J. Infect. Dis.* 180: 892-895 (1999) ("Paoletti (1999)").

Claims 7 and 45 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong, in view of Paoletti (1994), and in further view of an abstract of article by Wessels et al. published in *J. Infect. Dis.* 171: 879-884 (1995) ("Wessels").

Claims 8 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong, in view of Paoletti (1994) and Wessels, and in further view of an article by Michon et al. in "Streptococci and the Host. (Ed) Horaud et al. Plenum Press, New York, p. 847-850, 1997 ("Michon") and an article by Laude-Sharp et al. in Abstracts of the 97th General Meeting of the American Society for Microbiology, Miami Beach, FL, page 251, #E-62, 1997 ("Laude-Sharp").

B. Amendments to the Specification

Applicants have amended ¶ [19] of the specification to remove a drafting error. No new matter has been added by this amendment to the specification.

C. Claim Amendments

In this paper, Applicants have amended claims 1 and 42 to specify that "each polysaccharide of the at least three types of purified bacterial caspular polysacchride has a molecular weight in the range of 80 - 120 kDa." Support for this amendment is found in the originally filed specification, p. 2, lines 25-26, and in original claim 9.

Claims 2, 3, 4, 6, 11, 42, and 44 have also been amended to improve consistency in the claim language and to correct minor grammatical errors. Applicants respectfully submit that no new matter has been added by these amendments.

C. Rejections Under 35 U.S.C. § 112

1. Rejection of Claim 42 Under 35 U.S.C. § 112, ¶ 1 (new matter)

Applicants respectfully traverse the rejection of claim 42 under 35 U.S.C. § 112, ¶ 1. Briefly, the Office Action's new matter rejection appears to be based on a misinterpretation of a passage in Applicants' specification. As discussed below, the passage in question actually does provide support for the claim amendments presented in Applicants' previous paper, despite the Office Action's statements to the contrary. Accordingly, the rejection of claim 42 under 35 U.S.C. § 112, ¶ 1 should be withdrawn.

In Applicants' previous paper, claim 42 was amended to recite, *inter alia*, that the claimed "pharmaceutical composition" comprises "multivalent conjugate molecules." This amendment was made in response to the Examiner's remark that she interpreted the previous version of claim 42 to contain only one multivalent conjugate molecule. As amended in Applicants' previous response, claim 42 read as follows:

> 42. A pharmaceutical composition comprising
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> a pharmaceutically acceptable carrier; and
>
> multivalent conjugate molecules, wherein each multivalent conjugate molecule comprises a carrier protein with at least three different types of purified bacterial capsular polysaccharides covalently linked to said carrier protein,
>
> wherein each type of said at least three different types of purified bacterial capsular polysaccharides is obtained from a different serotype of a bacteria by treating the bacteria with an enzyme or base, directly followed by separation to isolate said at least three different types of purified bacterial capsular polysaccharide, and
>
> wherein the multivalent conjugate molecules are present in said composition in an amount sufficient to elicit protective antibodies against the three different types of bacterial capsular polysaccharides.

[see amendment filed October 29, 2007 ("the October 29, 2007 response"), pp. 8-9]. Applicants cited paragraphs [67] and [87] of the original specification as examples of passages in Applicants' disclosure that support the phrase "multivalent conjugate molecules" [the October 29, 2007 response pp. 14-15]. In particular, Applicants pointed out that ¶ [67] states that "[t]he conjugate molecules of the invention are typically administered as a pharmaceutical composition in a pharmacologically acceptable carrier" (emphasis added), which supports the recitation that the claimed "pharmaceutical composition" contains more than one conjugate molecule. Further, Applicants noted that ¶ [87] discloses that "one dose for a CD1 female mouse is 1 μg of conjugated-type polysaccharide, which must contain more than one conjugate molecule" [the October 29, 2007 response, pp. 14-15].

In response to these amendments, the Office Action asserts that Applicants' specification is limited to a mixture of monovalent conjugates, and there is no support for a "pharmaceutical composition" comprising "multivalent conjugate molecules." [Office Action, p. 5]. Citing ¶ [87] of Applicants' specification, the Office Action states that "paragraph [87] describes the induction of protective immune response of a tetravalent chimeric vaccine, i.e., a mixture of *monovalent* conjugates" and is "not supporting of the now recited limitations" [Office Action, p. 5 (emphasis in the original)].

Applicants disagree with the Office Action's characterization of ¶ [87] of the specification, as it appears to be based upon a misreading of the text contained therein. Paragraph [87] of the specification concerns a comparative study involving both a "tetravalent chimeric conjugate" (i.e., an example of the "multivalent conjugates" recited in claim 42) and a "mixture of monovalent conjugates." This can be seen by considering the highlighted portions of ¶ [87] shown below.

> [87] The multivalent conjugate was tested for the ability to elicit a protective immune response. The efficacy of the tetravalent chimeric conjugate prepared as described herein was evaluated in comparison to a tetravalent vaccine mixture comprising, a Ia/Ib/III/V combination vaccine, i.e., a mixture of monovalent conjugates. Animals (CD1 female mice) were inoculated with the chimeric vaccine or the combination tetravalent vaccine mix. Each animal received 1 μg of each of the conjugated type-polysaccharide, at days 0 and 21. Vaccines were adsorbed on Aluminum hydroxide (Superfos, Denmark). Mice were inpregnated at day 21. Neonates were challenged 48 hours following birth with GBS type Ia, GBS type Ib, GBS tpe III or GBS type V. The results (FIG. 11) show that the chimeric conjugate was as effective as the tetravalent vaccine mixture in eliciting a protective immune response.

Thus, this passage concerns a comparison of a "tetravalent chimeric conjugate" with a "tetravalent vaccine mixture…i.e., a mixture of monovalent conjugates." In view of this disclosure, the Office Action's characterization of ¶ [87] as being limited to a "mixture of monovalent conjugates" is factually inaccurate.

Moreover, Applicants respectfully direct the Examiner to ¶ [38] of the originally filed specification, which provides further support that the compositions recited in claim 42 are not a mere mixture of monovalent conjugates, but instead contain molecules in which a plurality of polysaccharides are attached to a single protein:

> A "multivalent" molecule or vaccine comprises more than one antigenic epitope. For example, multivalent vaccines of the invention often comprise at least three different bacterial polysaccharides conjugated to a single carrier protein. Such a vaccine therefore comprises four antigenic determinants and is a tetravalent vaccine [original specification, ¶[38]].

In view of the foregoing remarks, Applicants respectfully submit that the originally filed specification fully supports claimed chimeric "multivalent conjugate molecules" and the rejection under 35 U.S.C. § 112, ¶ 1 should be withdrawn.

2. Rejection of Claims 1-11, 42-46 and 52 Under 35 U.S.C. § 112, ¶ 1 (new matter)

Applicants respectfully traverse the rejection of claims 1-11, 42-46, and 52 under 35 U.S.C. § 112, ¶ 1. In making this rejection, the Office Action contends that "the specification lacks descriptive support for 'different types' of purified bacterial capsular polysaccharide" and also "lacks support for the limitation 'directly followed by separation to isolate said…different types of purified capsular polysaccharide.'" [Office Action, p. 6]. However, as discussed below, the claim language in question is fully supported by the specification as originally filed. Accordingly, the rejection should be withdrawn.

In concluding that "the specification lacks descriptive support for 'different types' of purified bacterial capsular polysaccharide," the Office Action states that "[t]he generic limitation 'different types of purified capsular polysaccharide' encompasses, for example, O-acetylated purified bacterial capsular polysaccharide, non-O-acetylated purified bacterial capsular polysaccharide, and de-N-acetylated purified bacterial capsular polysaccharide types resulting from base treatment." [Office Action, p. 6]. From this statement, it appears that the Office Action is suggesting that these types of polysaccharides are encompassed by the scope of the claims, yet do not find support in the specification as originally filed. To the extent that this is the view adopted by the Office Action, Applicants disagree and note that the originally filed specification provides support for the use of both native and modified forms of bacterial polysaccharides. For instance, ¶ [53] of the original specification states that "[t]he polysaccharides that are incorporated into a conjugate multivalent molecule of the invention include polysaccharide derivatives, i.e., modified polysaccharides, as well as native forms purified from bacteria." [original specification, ¶ [53] (emphasis added)]. Paragraph [53] further states that "[v]arious modifications of bacterial capsular polysaccharides are well known in the

art and include such modifications as N-propionylation and de-O-acetylation." [Id.]. Paragraph [54] of the original specification discloses various methods of obtaining modified bacterial capsular polysaccharides, including type B polysaccharides from *Neisseria Meningitidis* using C_3-C_8 N-acyl-substituted polysaccharide derivatives, N-propionylated type B derivatives, and de-O-acetylated group C meningococcal polysaccharides. Additionally, support for the phrase "different types of purified bacterial capsular polysaccharide" is found in ¶ [77] of the original specification, which discloses purification of GBS polysaccharides from strains Ia, Ib, II, III, and V, and in ¶¶ [78]-[79], which disclose a mixture of type Ia, Ib, II, III, and V GBS polysaccharides that are oxidized and conjugated to a carrier protein. In view of these exemplary passages in Applicants' specification, Applicants respectfully disagree with the Office Action's conclusion that the phrase "different types of purified bacterial capsular polysaccharide" is not supported by the specification.

Furthermore, Applicants respectfully disagree with the Office Action's conclusions that (1) "the specification lacks support for the limitation 'directly followed by separation to isolate said…different types of purified capsular polysaccharide'" [Office Action, p. 6]; and that (2) "[t]reatment of the bacteria with an enzyme or a base directly followed by separation would be expected to result in an isolated capsular polysaccharide, but not a purified capsular polysaccharide" [Office Action, p. 6]. Applicants direct the Examiner to ¶¶ [55]-[56] of the original specification, which describe methods of obtaining bacterial capsular polysaccharides by treatment with enzymes or base, followed by separation processes (e.g., differential precipitation, chromatography, and ultrafiltration) to remove proteins and nucleic acids and to produce purified capsular polysaccharides. Additionally, Applicants direct the Examiner to Example 1 of the original specification, which discloses base treatment of GBS

bacteria directly followed by ultrafiltration to remove proteins and nucleic acids. [see original specification, ¶[77]].

In view of these passages in the original specification, Applicants submit that the claim language in question is fully supported. Accordingly, Applicants request reconsideration and withdrawal of this ground of rejection.

3. Rejection of Claim 52 under 35 U.S.C. §112, ¶1

Applicants respectfully submit that this rejection is now moot in view of the cancellation of this claim. Accordingly, Applicants request reconsideration and withdrawal of this ground of rejection.

D. Rejections Under 35 U.S.C. § 112, ¶ 2

On pages 8-9 of the Office Action, the Examiner sets forth ten claim rejections under 35 U.S.C. §112, ¶2, which are enumerated as paragraphs (a) - (j). These claim rejections concern antecedent basis for the recited claim language.

Applicants respectfully submit that these rejections are moot in view of the claim amendments presented in the claim listing that begins on page 2 of this paper. Accordingly, Applicants respectfully request reconsideration and withdrawal of these grounds of rejection.

E. Rejections under 35 U.S.C. § 103(a)

1. Applicants' Claims 1, 2, 5, 6, 10, 11, 42 and 44 Are Patentable over Chong in view of Paoletti (1994)

Applicants respectfully traverse the rejection of claims 1, 2, 5, 6, 10, 11, 42 and 44 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Chong, in view of Paoletti (1994). Briefly, the combination of references fails to teach or suggest all of the claim elements of Applicants' invention. Accordingly, the rejection should be withdrawn. See In re Royka, 490 F.2d 981, 985 (CCPA 1974) (stating that obviousness requires a suggestion of all limitations in a claim).

Applicants' independent claims 1 and 42, as amended, specify that "each polysaccharide of the at least three types of purified bacterial caspular polysaccharides has a molecular weight in the range of 80 - 120 kDa". However, neither Chong nor Paoletti (1994) teaches or suggests this claimed molecular weight range. To the contrary, Chong teaches away from this claimed molecular weight range by reporting that capsular polysaccharides obtained from *Streptococcus pneumoniae* or *N. meningitides*, and which have starting molecular weights greater than 50 kDa and greater than 10 kDa, respectively, are subjected to acid hydrolysis to produce oligosaccharides with a mean molecular weight of 2 to 5 kDa [see Chong, ¶[0062], [0063]]. These 2 to 5 kDa polysaccharide fragments, which are used in Chong's immunogenic molecules [see Chong, ¶[0016]], do not have a molecular weight that falls within the claimed molecular weight range of 80 - 120 kDa. Furthermore, Chong reports that its acid hydrolysis-based procedure may be generally used for other bacteria, stating a "[s]imilar procedure may be used for capsular polysaccharides of other bacteria" [Chong, ¶[0064]].

Furthermore, Paoletti (1994) does not teach or suggest a "multivalent conjugate" with the claimed polysaccharide molecular weight range of 80 - 120 kDa. Instead, Paoletti (1994) only reports mixtures of monovalent vaccines which have polysaccharides with either relatively low molecular weights [e.g., polysaccharides with a molecular weight of 6 to 8 kDa, see Paoletti (1994), p. 3237, col. 2, lines 30-31] or relatively high molecular weights [e.g., having a relative molecular mass (M_r) of 200,000 or > 10^6, see Paoletti (1994), Table I].

In view of the foregoing, Applicants respectfully assert that the combination of Chong and Paoletti (1994) fails to teach or suggest all of the features of the claimed invention. However, in making these arguments, Applicants are mindful that claim 9 (now cancelled) required the claimed bacterial capsular polysaccharides to be "of a size between 80 and 120 kilodaltons" and that claim 9 had been rejected over a combination of Chong, Paoletti (1994) and Wang. Nonetheless, Applicants maintain that even if Chong and Paoletti (1994) are combined with Wang, the resulting combination would not teach or suggest the invention now recited in claims 1 and 42, as amended. Wang is directed to the use of ozone to depolymerize Group B Streptococcus capsular polysaccharides, but does not teach or disclose polysaccharides within the claimed molecular weight range. To the contrary, Wang reports a study in which a 61 kDa polysaccharide fragment, which does not fall within the claimed range, is subjected to ozonolysis to produce polysaccharide fragments having an average molecular mass of 10 kDa or less [see Wang, p. 6585, col. 2, lines 4-6, and p. 6586, sentence bridging columns 1 and 2]. Thus, even if Wang is combined with Chong and Paoletti (1999), the resultant combination does not teach or suggest a "multivalent conjugate molecule" with a "polysaccharide" having "a molecular weight in the range of 80 - 120 kDa" as recited in Applicants' independent claims 1 and 42.

Accordingly, the rejections under 35 U.S.C. §103(a) of claims 1 and 42, as well their corresponding dependent claims, should be withdrawn.

2. The Rejection of Claims 9 and 52 over Chong in view of Paoletti (1994) and Wang Is Moot

Applicants respectfully submit that the rejection of claims 9 and 52 over Chong, in view of Paoletti (1994) and Wang is moot in view of the fact that these claims have been cancelled. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

3. Applicants' Claims 3 and 4 Are Patentable over Chong in view of Paoletti (1994) and Paoletti (1999)

Claims 3 and 4 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong in view of Paoletti (1994) and further in view of Paoletti (1999). However, Chong and Paoletti (1994) do not teach or suggest all of the claimed features of independent claim 1, from which claims 3 and 4 depend. For example, as noted above, Chong and Paoletti (1994) do not teach or suggest polysaccharides with a molecular weight in the range of 80 -120 kDa, as recited in claim 1. Paoletti (1999) does not alleviate these shortcomings of Chong and Paoletti (1994), as Paoletti (1999) only uses type VI and VIII GBS polysaccharides with a relative molecular weight of 200,000 in its studies. Even though these polysaccharides are subjected to oxidation using sodium periodate [see Paoletti (1999), p. 892, col. 2, 3rd full paragraph; p. 893, col. 1, second full paragraph], the oxidation process does not cleave the polysaccharide backbone to produce polysaccharides in the claimed molecular weight range. As the Examiner will appreciate, in the type VI and VIII GBS polysaccharides used by Paoletti

(1999), the sialic acid residues that contain vicinal diols susceptible to periodate oxidation reside on side chains of the polysaccharide, and are not incorporated into the main backbone. Accordingly, even if the sialic acid residues on Paoletti (1999)'s polysaccharides, which have relative molecular weight of 200,000, are oxidized 41%, 50% or 100% by periodate as reported by Paoletti (1999) [Paoletti (1999), p. 892, col. 2, 3rd full paragraph; p. 893, col. 1, second full paragraph], the resultant oxidized polysaccharides would be expected to have the same chain length and nearly the same molecular weight. Accordingly, Applicants respectfully submit that the molecular weight of Paoletti (1999)'s polysaccharides would not fall within the claimed molecular weight range of 80 - 120 kDa, and the combination of Chong, Paoletti (1994) and Paoletti (1999) fails to disclose all of the features of the claimed invention.

4. Applicants' Claims 7 and 45 Are Patentable over Chong in view of Paoletti (1994) and Wessels

Claims 7 and 45 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong in view of Paoletti (1994), and further in view of Wessels. However, as noted above, Chong and Paoletti (1994) do not teach or suggest all of the features of the claimed invention, such as a "multivalent conjugate molecule" comprising polysaccharide having "a molecular weight in the range of 80 - 120 kDa." Wessels does not alleviate this deficiency of Chong and Paoletti, as Wessels (i.e., the abstract relied upon by the Office Action) is silent on the molecular weight range of the polysaccharides used in its study. Moreover, Applicants note that the full article by Wessels, which has been submitted in an Information Disclosure Statement with this paper, does not teach or suggest the claimed polysaccharide molecular weight range. Instead, the full article by Wessels only states that the polysaccharides that were coupled to tetanus toxoid had a relative molecular weight (Mr) of 200,000 (see p. 881,

line 3 of the first paragraph in the Results section). Thus, Applicants respectfully submit that the combination of Chong, Paoletti (1994), and Wessels fails to teach or suggest all of the features of claims 7 and 45, and the rejection of these claims under 35 U.S.C. § 103(a) should be withdrawn.

5. Applicants' Claims 8 and 46 Are Patentable over Chong in view of Paoletti '94 and Wessels and Further in view of Michon and Laude-Sharpe

Claims 8 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong in view of Paoletti (1994), Wessels, Michon, and Laude-Sharp. However, as noted above, Chong, Paoletti (1994), and Wessels do not teach or suggest all of the features of the claimed invention, such as a "multivalent conjugate molecule" comprising polysaccharide having "a molecular weight in the range of 80 - 120 kDa." The Office Action's reliance upon Michon and Laude-Sharp do not cure these deficiencies of Chong, Paoletti (1994), and Wessels, as none of these references teach or suggest a "multivalent conjugate molecule" comprising polysaccharide having "a molecular weight in the range of 80 - 120 kDa." Accordingly, the rejection of claims 8 and 46 over Chong, Paoletti (1994), Wessels, Michon, and Laude-Sharp should be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-3732, Order No. 13564-105038US1.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-3732, Order No. 13564-105038US1.

Respectfully submitted,
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